28-Day Dosing with Avexitide Improves Hyperinsulinemic Hypoglycemia in Patients with Severe, Refractory Post-Bariatric Hypoglycemia: The PREVENT Study

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Disclosures

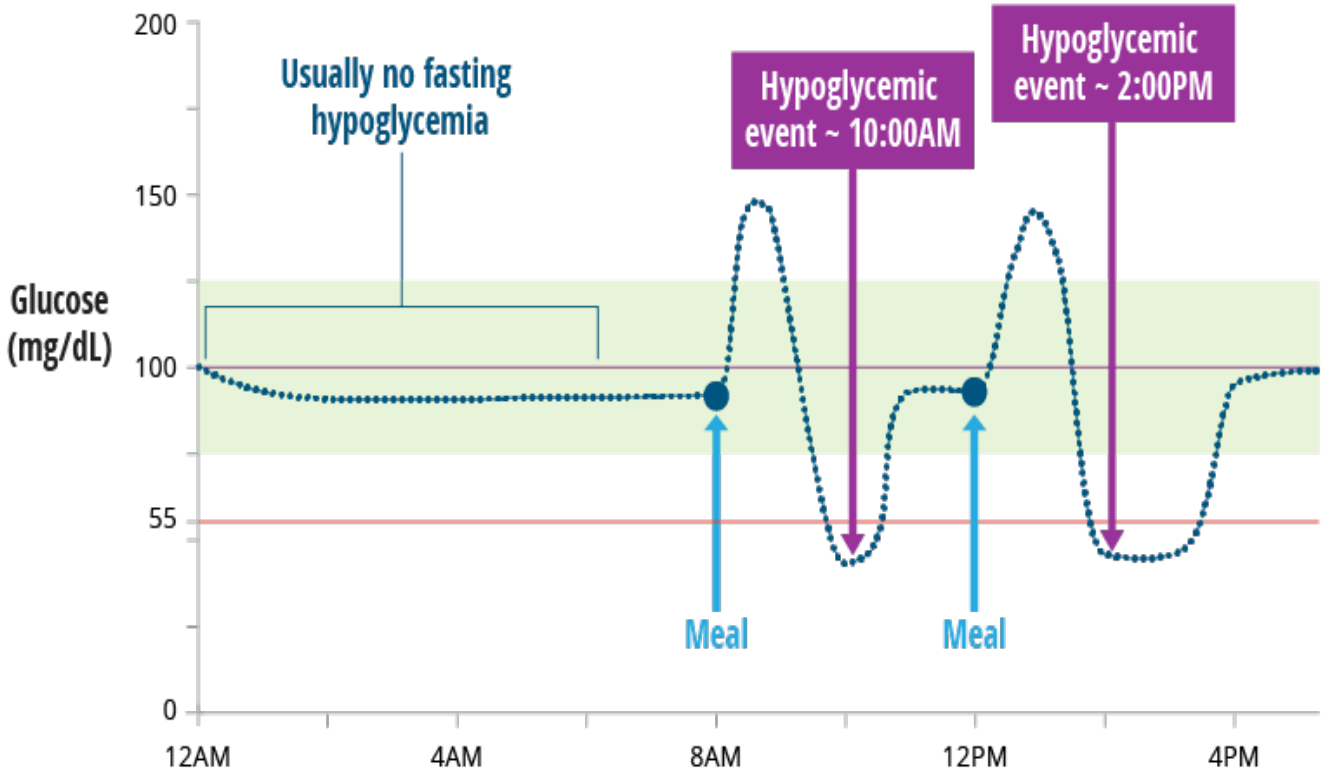
I have consulted for XOMA and Xeris Pharmaceuticals and have been a site investigator for Eiger Pharmaceuticals.

Sample Case

- 50 year-old woman with obesity (BMI 45 kg/m^2)
- Underwent Roux-en-Y gastric bypass and lost nearly 100 pounds within a year
- New onset postprandial hypoglycemia 2 years after surgery
- Severe episodes leading to confusion, visits to the ED and no longer able to drive or work due to risks to self and/or others
- Prior workup included
  - 75 gram oral glucose tolerance test: glucose of 87 mg/dL at baseline, 33 mg/dl at 120 min with confusion
  - Unremarkable CT abdomen
  - Normal ACTH stimulation test
  - No focal hypersecreting insulin producing lesion on selective arterial calcium stimulation test

Post-Bariatric Hypoglycemia (PBH)

- Normal fasting glucose
- Hypoglycemia 1-3 h after eating
- Often debilitating
- Glucose <55 mg/dL may trigger neuroglycopenic symptoms (e.g. dizziness, blurred vision, syncope)
- May impact 5-10%[1,2] of Roux-en-Y patients
- No approved pharmacotherapy; many patients refractory to diet and off-label meds

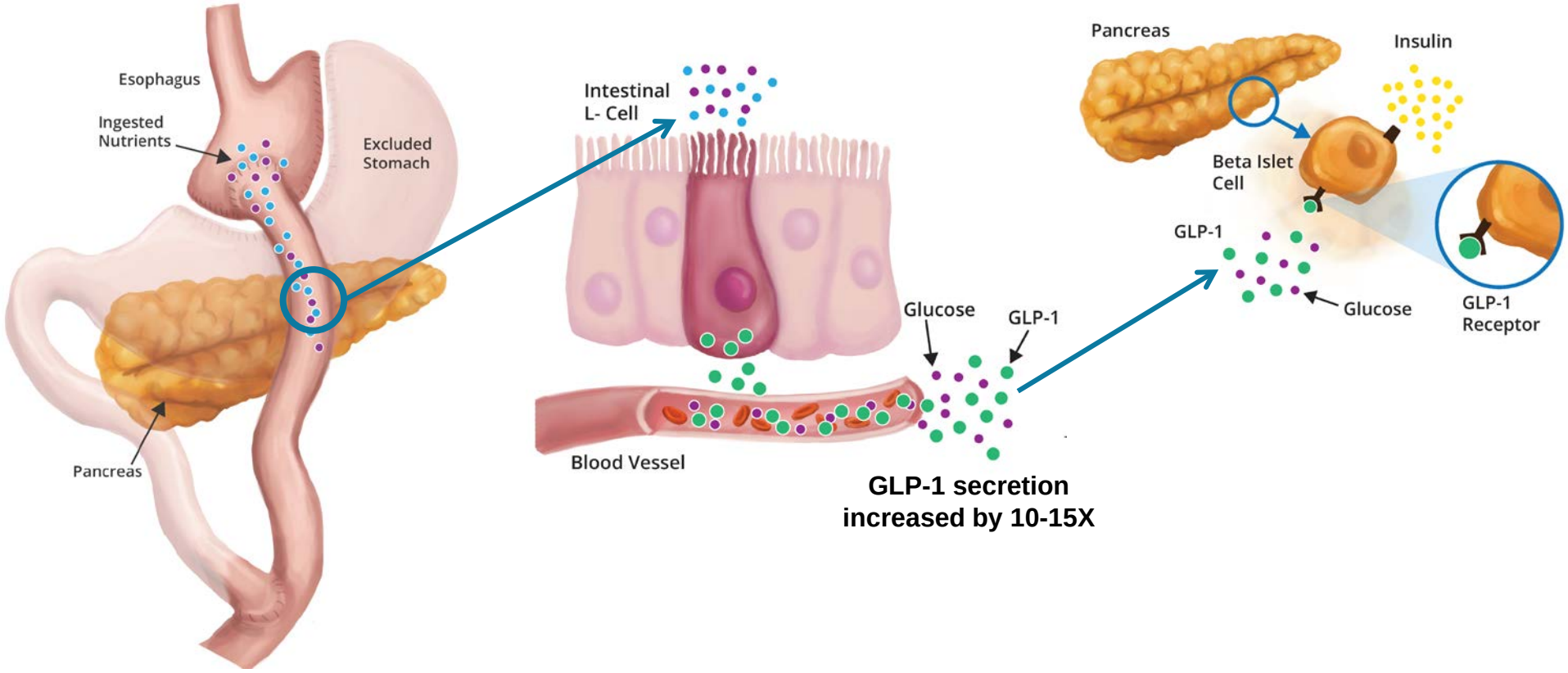


[1] Gribsholt et al. JAMA 2016; [2] Lee et al. Obesity 2015

Etiology of PBH: Critical Role of GLP-1

Altered Nutrient Transit Triggers an Exaggerated Incretin Effect via GLP-1

ALTERED NUTRIENT TRANSIT POST ROUX-EN-Y GASTRIC BYPASS → **HYPERSECRETION OF GLP-1** → **HYPERSECRETION OF INSULIN** → **SYMPTOMATIC HYPOGLYCEMIA**



GLP-1 secretion increased by 10-15X

Autonomic
- Sweating
- Shaking
- Palpitations
- Hunger

Neuroglycopenic
- Blurred vision
- Confusion
- Drowsiness
- Odd behavior
- Speech difficulty
- Incoordination
- Dizziness
- Inability to concentrate

Craig et al. Diabetes, Obesity and Metabolism 2018

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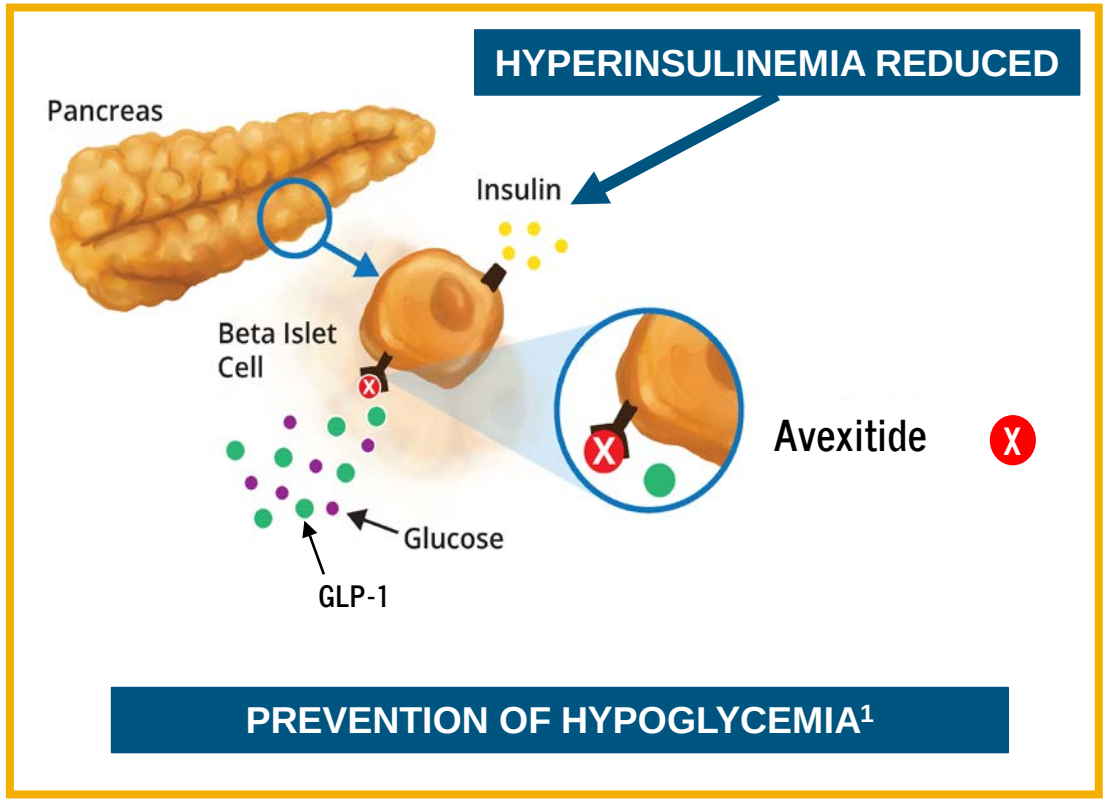
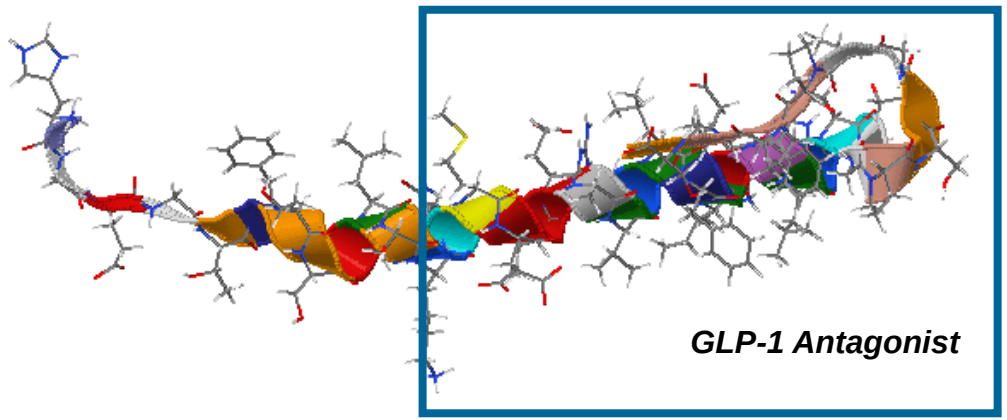
Pharmacologic Blockade of GLP-1 Receptor

A Targeted Therapeutic Approach Reduces Hyperinsulinemia and Prevents Hypoglycemia

Avexitide



Avexitide



- 31 amino acid fragment of exenatide (registered name for Byetta)
- A GLP-1 receptor antagonist
- Used as investigational agent
- >300 patients reported dosed worldwide[2]

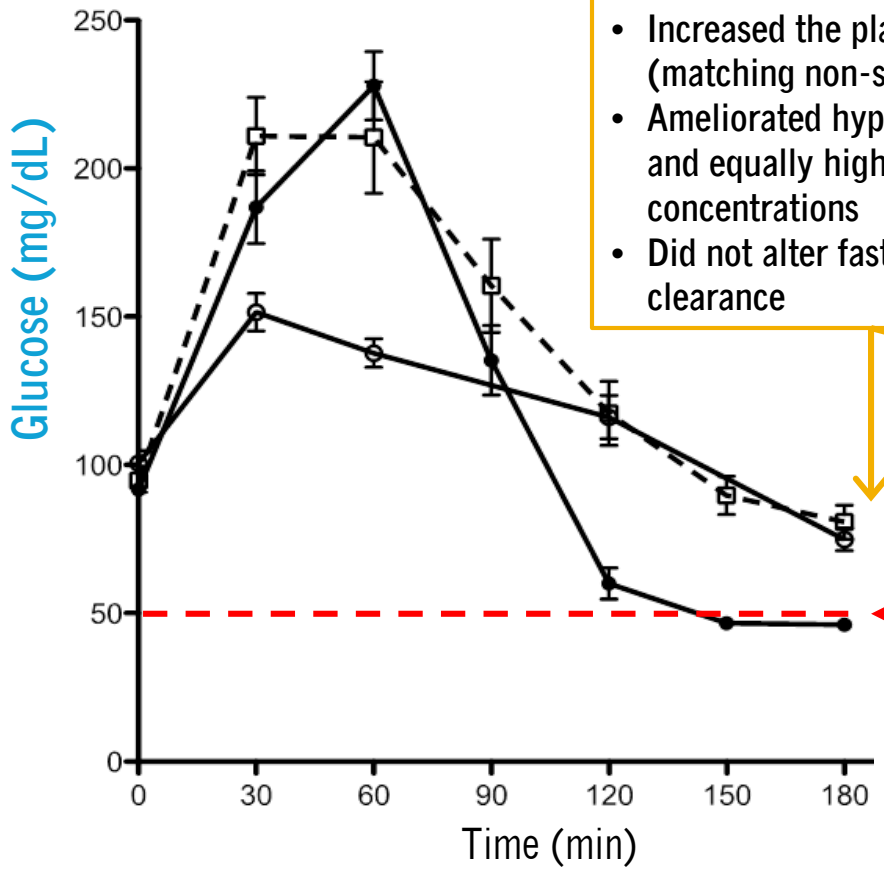
[1] Craig et al. Diabetes, Obesity and Metabolism 2018; [2] Clinicaltrials.gov

Placebo-Controlled Crossover IV Infusion Study

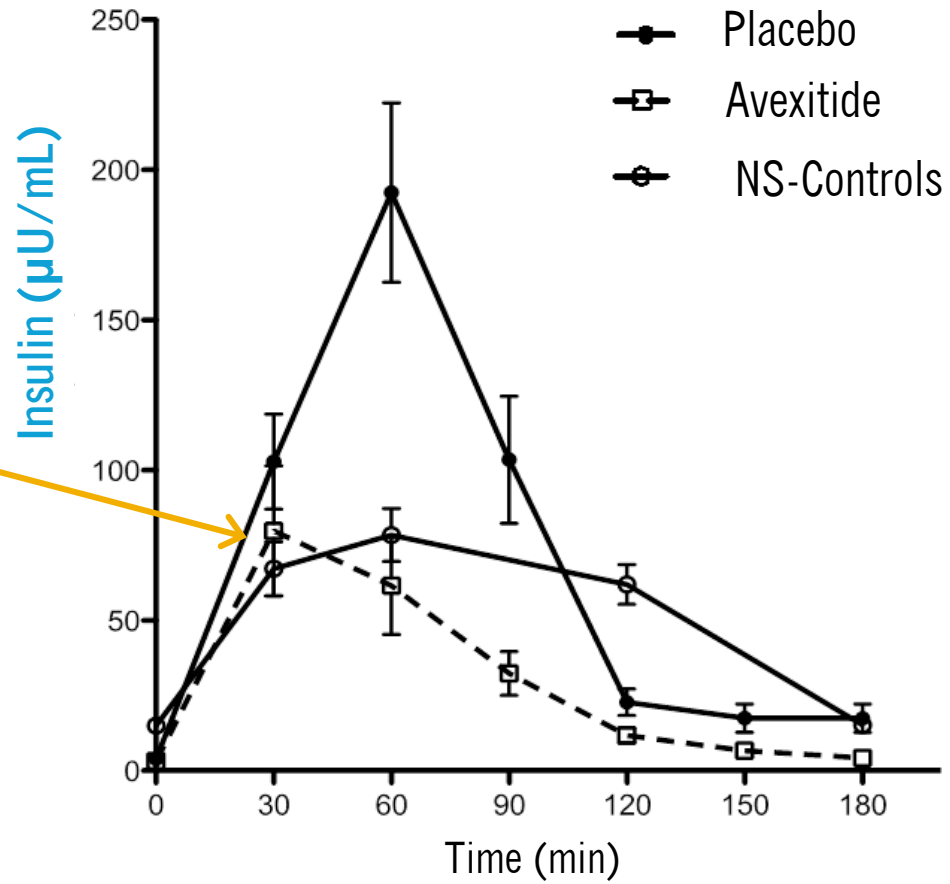
8 Patients with PBH Received Placebo or Avexitide Infusion During OGTT Provocation

Avexitide infusion:

- 100% reversal of hypoglycemia
- Increased the plasma glucose nadir by 70% (matching non-surgical controls)
- Ameliorated hyperinsulinemia despite earlier and equally high peak plasma glucose concentrations
- Did not alter fasting insulin or insulin clearance



Patients rescued at glucose ≤50 mg/dL

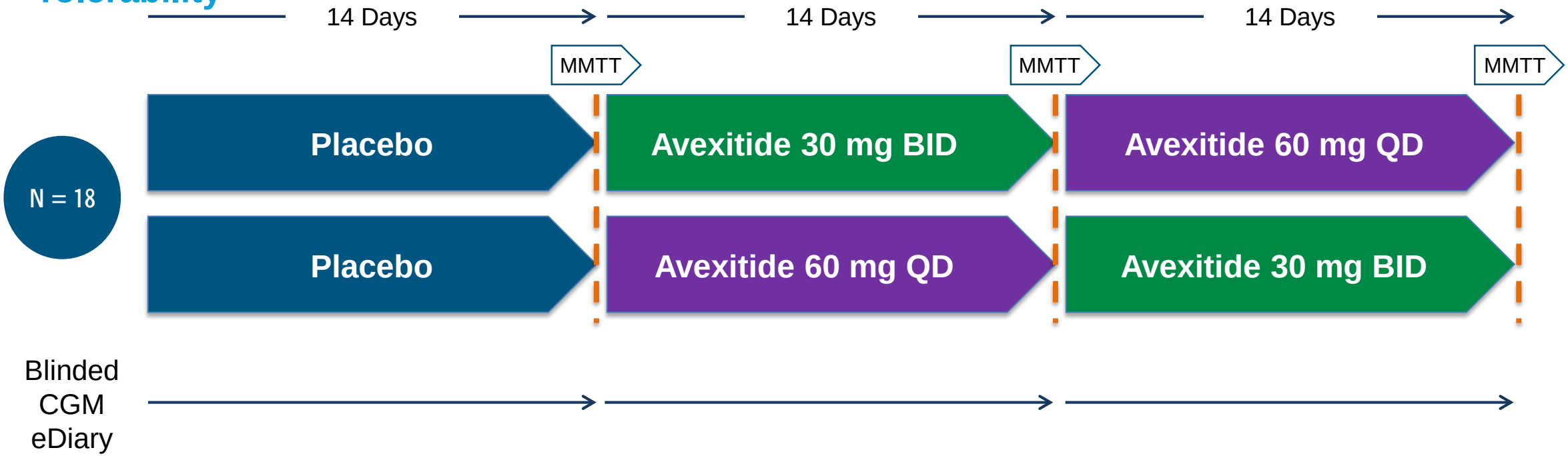


Craig et al. Diabetologia, 2017

A Phase 2, Multicenter, Randomized, Placebo-Controlled Cross-over Study to Assess the Efficacy and Safety of Avexitide in Patients with PBH

28-Day, Phase 2 Study

Goal: Demonstrate Durability of Effect, Define Dose, Safety, Tolerability



Primary Efficacy Endpoint: Magnitude of postprandial hypoglycemia defined as the plasma glucose nadir during MMTT provocation

Participant Characteristics

Characteristic	30 BID – 60 QD	60 QD – 30 BID	Overall
n	8	10	18
Age (years)	45.5 (7.45)	43.4 (12.04)	44.3 (10.04)
Sex, # female (%)	8 (100)	10 (100)	18 (100)
BMI (kg/m^2)	30.01 (3.06)	29.28 (4.87)	29.61 (4.07)
History of LOC due to PBH, # (%)	3 (37.5)	5 (50.0)	8 (44.4)
History of Seizure due to PBH, # (%)	0 (0.0)	2 (20.0)	2 (11.1)
History of hospitalization due to PBH, # (%)	1 (12.5)	2 (20.0)	3 (16.7)
Frequency of Symptoms of Hypoglycemia			
Daily, # (%)	3 (37.5)	4 (40.0)	7 (38.9)
Weekly, # (%)	5 (62.5)	5 (50.0)	10 (55.6)
Following medical nutrition therapy, # (%)	8 (100.0)	10 (100.0)	18 (100.0)
History of pharmacotherapy for PBH, # (%)	5 (63.0)	10 (100.0)	15 (83.0)
History of surgery for PBH, # (%)	1 (5.6)	2 (11.1)	3 (16.7)

95%

Values represent mean (SD) or number (%) as applicable

Metabolic Responses to MMTT

Significantly Reduced Hyperinsulinemic Hypoglycemia; Reduced Requirement for Rescue

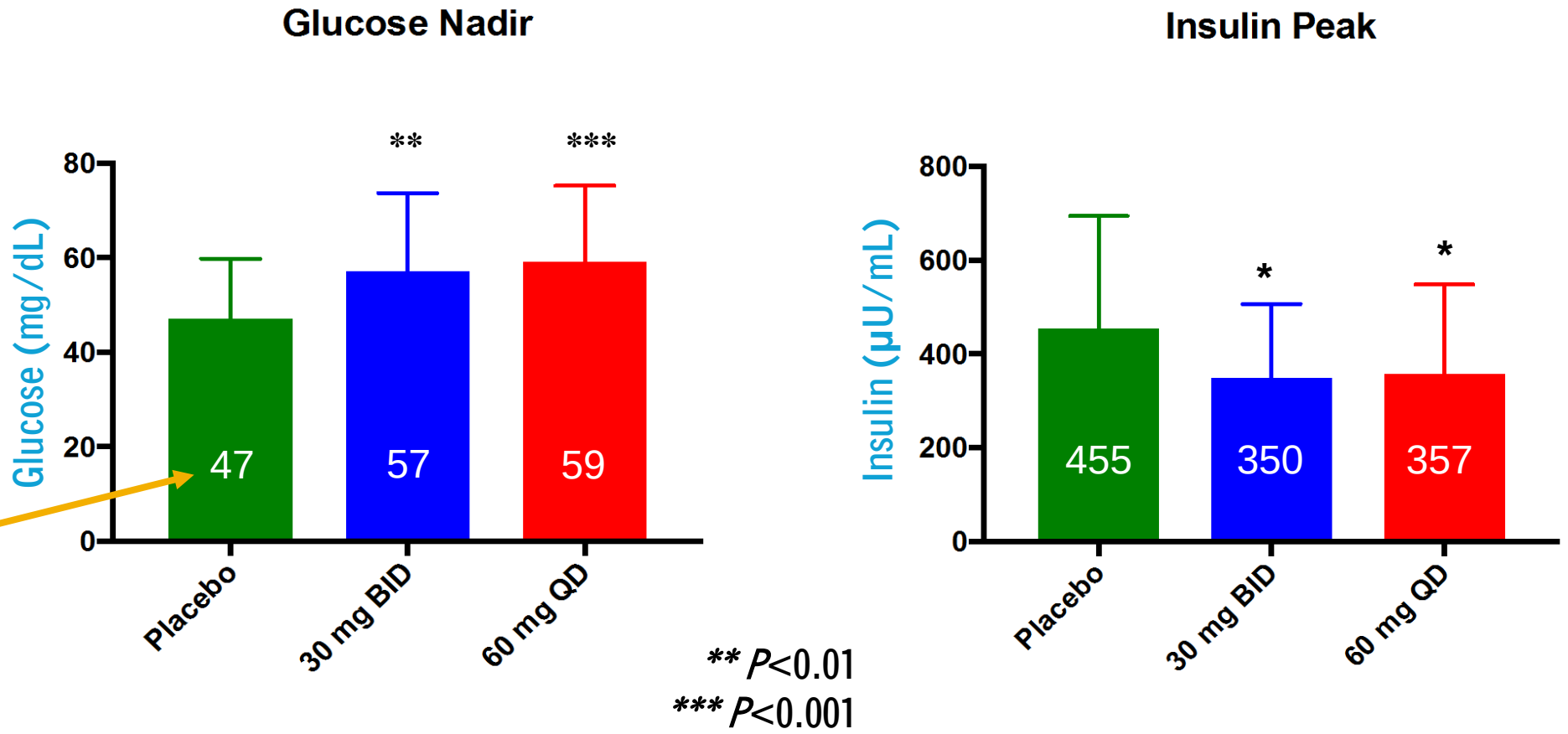
True placebo nadir likely lower due to higher rate of rescue:

Rescue was administered at the earlier of:

- Glucose ≤ 50 mg/dL + neuroglycopenia

OR

- Glucose **≤ 40 mg/dL +/- neuroglycopenia**



** *P*<0.01
*** *P*<0.001

Clinical Improvements in the Outpatient Setting

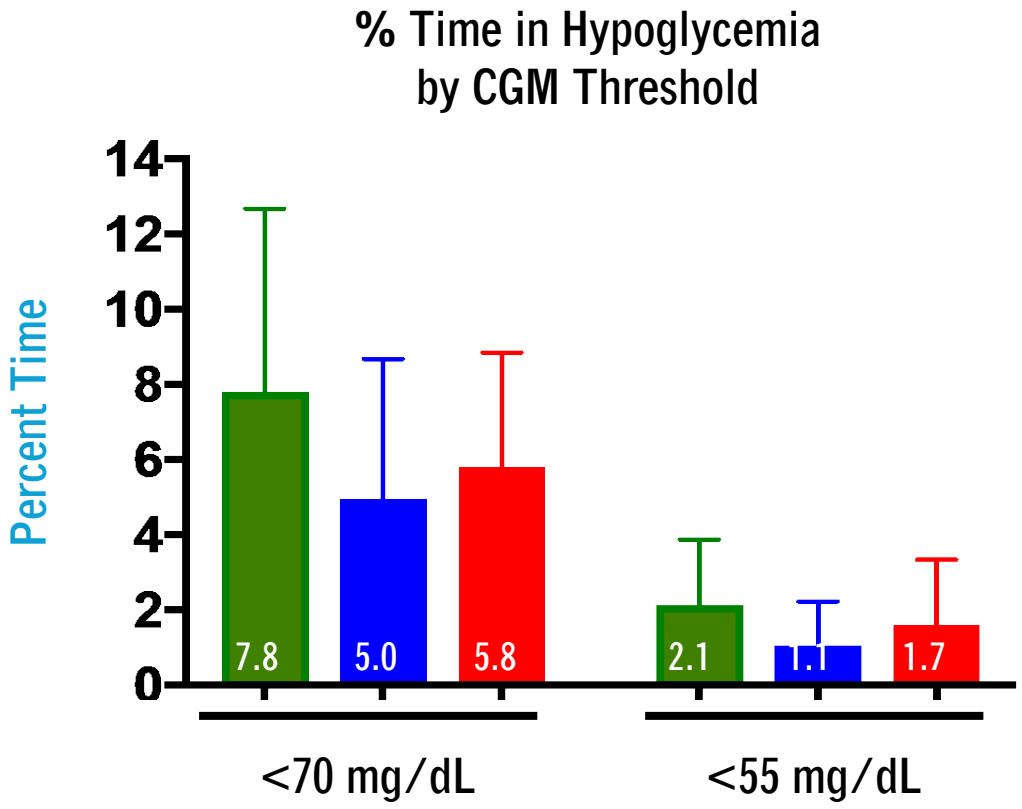
Reduction in Rates[1] of Hypoglycemia, Severe Hypoglycemia and Rescue as Collected by SBGM + eDiary

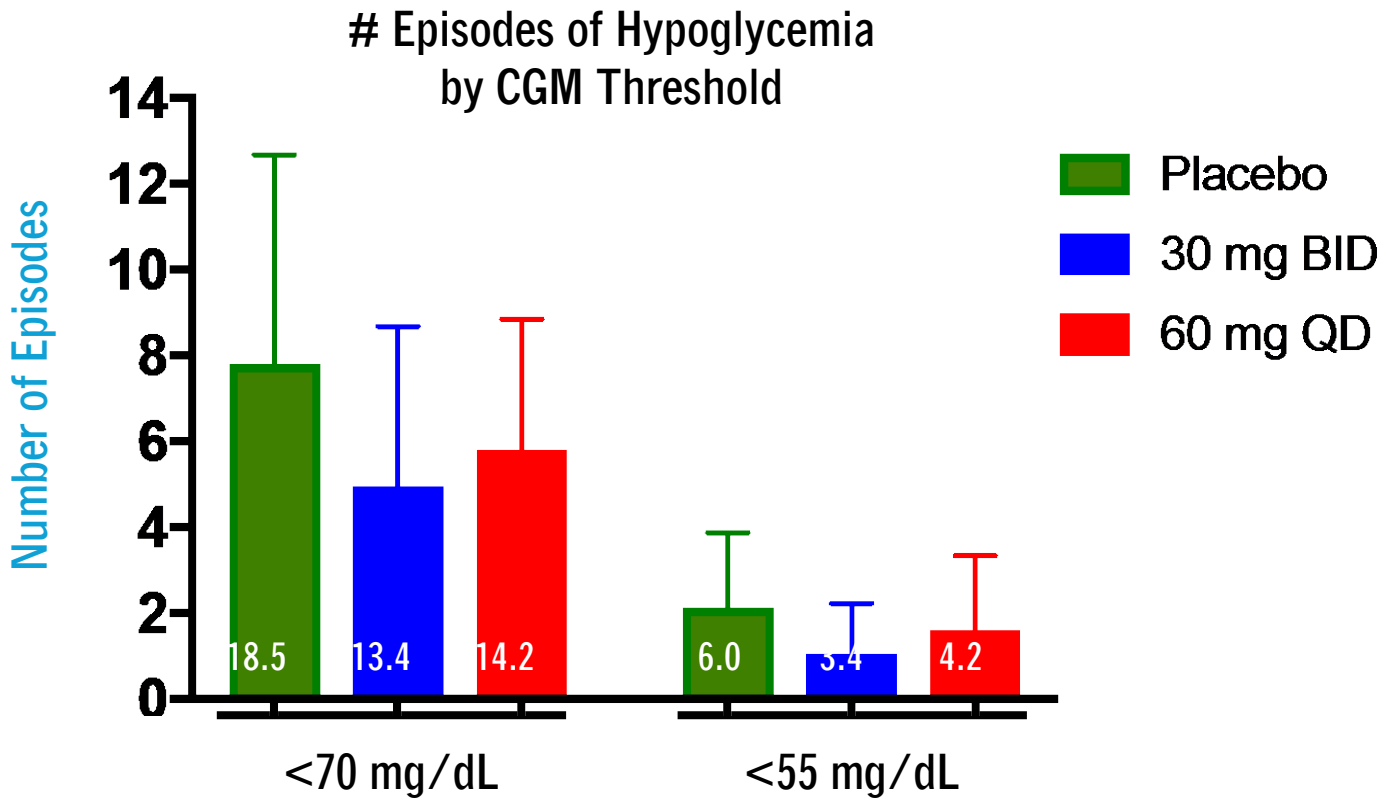
	Number of Episodes in 14 Day Period		
	Placebo	**30 mg BID**	**60 mg QD**
Rate of Hypoglycemia[2]	4.03	2.81	1.56
Change from Placebo	NA	-1.24 (**p=0.0720**)	-2.51 (**p=0.0014**)
Rate of Severe Hypoglycemia[3]	2.36	1.45	0.99
Change from Placebo	NA	-0.89 (**p=0.0267**)	-1.35 (**p=0.0020**)
Rate of Rescue[4]	4.87	3.34	1.83
Change from Placebo	NA	-1.60 (**p=0.0614**)	-3.13 (**p=0.0013**)

[1] Rate is defined as number of episodes in a 14 day period
[2] Hypoglycemia is defined as hypoglycemia symptoms confirmed by SBGM concentrations of <70 mg/dL
[3] Severe hypoglycemia is defined as neuroglycopenic symptoms confirmed by SBGM concentrations <55 mg/dL
[4] Rescue is defined as requiring self- or third-party administration of oral or g-tube intake to prevent or treat hypoglycemia

Glycemic Improvements in the Outpatient Setting

Reduction in Diurnal[1] % Time and # of Episodes[2] <70 and <55 mg/dL as Measured by CGM





[1]Diurnal is defined as 8AM to midnight.
[2]Episodes are per 14-day period, and are defined as CGM values sustained below threshold for at least 10 min within in a 3-hour period.

SAFETY AND TOLERABILITY

- Avexitide was well-tolerated
- No treatment-related SAEs and no participant withdrawals
- One non-treatment related SAE
- AEs were typically mild to moderate in severity and transient
- Most common AEs were injection site bruising, nausea, headache
  - All occurred with higher frequency during placebo than active treatment
- Low occurrence of development of anti-drug antibodies (ADA)
  - 1 of 18 participants showed low positive titers for ADA
  - No associated AEs and no apparent effect on efficacy

CONCLUSIONS

- GLP-1 plays a critical role in mediating hyperinsulinemic hypoglycemia in PBH
- Avexitide is a targeted therapeutic approach with POC demonstrated in 4 clinical trials
- 28-days of treatment in outpatient setting demonstrated clinically meaningful improvements:
    - Reductions in the magnitude of postprandial hyperinsulinemic hypoglycemia
    - Reductions in the rates of hypoglycemia and severe hypoglycemia
    - Reductions in the rates of rescue
    - Reductions in the percent time in hypoglycemia and number of hypoglycemic episodes
- Avexitide was well-tolerated, with no significant safety concerns
- Avexitide has shown consistent benefits across clinical and metabolic parameters

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PREVENT

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